SUMMARY OF BASIS FOR APPROVAL

Reference Numbers: 93-0253 and 97-0141

Biological Product Name: Pooled Plasma, Solvent/Detergent Treated

Manufacturer: V.I. Technologies, Inc. (VITEX)
155 Duryea Road
Melville, New York 11747 USA

Trade Name: VIPLAS/SD™

I. Indications for use

The indications for use of VIPLAS/SD™, Pooled Plasma, Solvent/Detergent Treated, are limited and include: treatment of patients with documented deficiencies of coagulation factors for which there are no concentrate preparations available, including congenital single-factor deficiencies of factors I, V, VII, XI and XIII, and acquired multiple coagulation factor deficiencies; reversal of warfarin effect; and treatment of patients with thrombotic thrombocytopenic purpura (TTP).

II. Dosage Form, Route of Administration and Recommended Dosage

VIPLAS/SD™ is supplied frozen in plastic bags containing 200 mL each, labeled with the ABO blood type. Following thawing, the product is to be administered intravenously with an adequate filter. The product should be used as soon as possible after thawing but no more than 24 hours after thawing, and the product is not to be refrozen once thawed.

Patients with deficiencies of coagulation factor(s)

VIPLAS/SD™ should be ABO compatible with the recipient's red cells. The amount of VIPLAS/SD™ required for normalizing hemostasis depends upon the patient and upon the circumstances. As a general guideline, it has been reported that plasma levels of between 0.1 and 0.2 u/mL (10% to 20% of normal) of most factors are hemostatic, except for factor XIII where 0.05 u/mL and prothrombin where 0.3 u/mL are reported to be hemostatic.

Patients with TTP

For the treatment of chronic TTP, an infused dose of 50-100 mL in children and up to 3 units for adults has been found to be satisfactory at preventing relapses; the dose is repeated as necessary, typically at 3-week intervals. For the treatment of acute TTP, more vigorous treatment is warranted, and exchanges of up to 2 plasma volumes of VIPLAS/SD™ daily, or as often as deemed necessary, are appropriate.

III. Manufacturing and Controls

A. Manufacturing

Pooled Plasma, Solvent/Detergent Treated, is a type specific (ABO Group) human plasma product treated with the solvent tri(n-butyl)phosphate (TNBP) and the detergent Triton X-100 to inactivate enveloped viruses (including HIV, HBV and HCV) that are found in blood and blood products. This product is prepared from the plasma of donors tested and found to be non-reactive for HBsAg, HIV-p24 antigen, and for antibody to HCV and HIV (1/2) by FDA-licensed tests.

The manufacturing process involves the following steps:

1) Plasma frozen within 15 hours of collection from volunteer donors is debagged, pooled and thawed at a temperature not to exceed 35°C. An upper limit of 2,500 individual units may be pooled together to form a single lot of the product.

2) $CaCl_2$ is added to a final concentration of 2 mM, and the product undergoes 1.0μm filtration and is transferred to a process tank.

3) The adjusted pooled plasma is virus-inactivated by the addition of 1% TNBP and 1% Triton X-100. The mixture is incubated at 31 $\pm$ 2°C for four hours.

4) TNBP and Triton X-100 concentrations are reduced by extraction with 5% soybean oil at 18 $\pm$ 4°C for 15 minutes, followed by clarification by sedimentation and filtration (1.0 and 0.45μm).

5) Residual TNBP and Triton X-100 are removed by reverse phase column chromatography on C-18 Gel at 20 - 25°C.

6) The product is filtered (1.0, 0.45 and 0.22μm), and the protein concentration is adjusted by ultrafiltration.

7) The product is sterile filtered (0.22μm) and aseptically filled into sterile bags which are then sealed, inspected, labeled and frozen.

The resultant product has been characterized, and is found to be similar biochemically to the starting material, human frozen plasma, as demonstrated on the following table. There are moderate decreases in Protein S and antiplasmin, and the highest molecular weight multimers of von Willebrand factor (vWF) are absent. The clinical significance of these differences, if any, is unknown.

Coagulation factor		Starting material, pooled plasma	S/D Plasma	Normal Range (u/mL or mg/mL)*	Release specification for final product
Prothrombin	u/mL	0.88 ± 0.03	1.00 ± 0.02	0.5 -1.5	
Factor V	u/mL	1.01 ± 0.02	1.06 ± 0.02	0.5 - 1.5	0.7
Factor VII	u/mL	1.01 ± 0.02	1.06 ± 0.02	0.5 - 1.5	0.7
Factor VIII	u/mL	0.92 ± 0.09	1.21 ± 0.3	0.5 - 1.5	
Factor IX	u/mL	1.10 ± 0.04	1.09 ± 0.09	0.5 - 1.5	
Factor X	u/mL	0.85 ± 0.04	1.01 ± .01	0.5 - 1.5	0.7
Factor XI	u/mL	1.01 ± 0.01	1.04 ± 0.01	0.5 - 1.5	0.7
Factor XIII	u/mL	1.18 ± 0.05	1.23 ± 0.06	0.5 - 1.5	0.7
Fibrinogen	mg/mL	2.46 ± 0.14	2.57 ± 0.25	1.5 - 4.0	1.8
ATIII	u/mL	0.80 ± 0.05	0.90 ± 0.02	>0.55	
Protein C**	u/mL	0.85 ± 0.02	0.77 ± 0.03	0.58- 1.64	
Protein S**	u/mL	0.96 ± 0.11	0.52 ± 0.03	0.56 - 1.68	
Factor Xa-like (S2222)	u/mL	0 ± 0	0.016 ± 0.005	<0.1	
Thrombin-like (S2238)	u/mL	0 ± 0	0.03 ± 0.02	<0.1	
Kallikrein-like (S2302)	u/mL	0.01 ± 0.01	0.03 ± 0.00	<0.1	
C1-inhibitor**	u/mL		0.82 ± 0.02	0.65 - 1.30	
Anti-Plasmin**	u/mL		0.48 ± 0.04	0.70 - 1.30	
Alpha-1-antitrypsin**	mg/mL		2.84 ± 0.11	1.20 - 2.70	
PT**	sec		11.5 ± 0.3	11 - 13	
aPTT**	sec		32.3 ± 0.6	25 - 40	

* Normal values reflect samples from 100 normal individuals assayed in the reference lab performing the analyses.
**-average ± standard deviation from 3 representative lots

Little or no coagulation factor activation is apparent during the solvent/detergent treatment process; thrombin/antithrombin III complexes and prothrombin split products measured by enzyme immunoassays are not increased. There are no significant perturbations of the normal ratio of plasma proteins and lipids in VIPLAS/SD™, and significant amounts of immunoglobulins remain in the final product. Studies have demonstrated that VIPLAS/SD™ injected into each of three rabbits did not elicit an antibody reactive with VIPLAS/SD™ that did not react with untreated plasma, as judged by the Ouchterlony technique or by neutralizing crossed immunoelectrophoresis.

The drug substance is manufactured at the Melville, New York facility of V.I. Technologies, Inc., where manufacturing, labeling, quality assurance and release takes place. The released product is then shipped to distribution centers.

V.I. Technologies, Inc. has entered into an agreement with the American Red Cross (ARC), specifying that all plasma to be manufactured into VIPLAS/SD™ is to be sourced from the ARC and that the distribution of the final product is to be exclusively through the ARC. The ARC has represented that VIPLAS/SD™ would be made available to other, non-ARC entities. V.I. Technologies, Inc. and the ARC have represented to CBER that they intend to incorporate an ARC contract warehousing facility into the

quarantine and release of raw material (plasma) and finished product. This plan is intended to supplement the storage capacity of the Melville, N.Y., facility.

Final container testing includes: visual inspection; protein composition by cellulose acetate electrophoresis; identity test by immunoprecipitation; coagulation factor assays for the following factors: factor V, factor VII, factor X, factor XI, factor XIII and fibrinogen; protein content by the Kjeldahl method; assays for sodium, potassium and hydrogen ion concentrations, TNBP and Triton X-100 content; ethyl alcohol content; isoagglutinin titers; antibodies to HIV (1/2) and HBsAg; endotoxin by limulus amoebocyte lysate test; sterility; and general safety test in mice (21 CFR 610.11).

B. Stability Studies

The stability of six batches of VIPLAS/SD™ has been investigated for up to 24 months. Storage stability studies reveal maintenance of product coagulation factors when stored for 24 months at -30°C. Similar data has been generated for product stored for 18 months at -30°C followed by 6 months at -18°C, as well as 9 months at -30°C followed by 18 months at -18°C. The product is labeled with an expiration of one year when stored at -18°C.

Studies of the thawed material have indicated that it is stable for at least 30 hours at room temperature, and is labeled be administered within 24 hours of thawing.

C. Validation

The manufacturing process for VIPLAS/SD™ has been validated for consistency and robustness. Appropriate validation procedures were in place to ensure the proper installation, operation and performance of the systems involved in the production of VIPLAS/SD™. Major systems which were validated included: water for injection, heating, ventilation, and air conditioning systems (HVAC), C18 chromatography column, clean-in-place system for fixed tanks, steam-in-place, water pre-treatment, and ultrafiltration systems, -30°C warehouse freezers, plasma bag freezers, steam generation, sterile bulk fill tanks, steam sterilizer, VIPLAS/SD™ process tanks, temperature control units, and manual cleaning procedures.

Assays of the drug substance and final container material have been validated for accuracy, precision and reproducibility. All final container lots have been shown to conform to requirements for identity, purity, potency and sterility according to 21 CFR Part 610. Three conformance lots have been submitted to CBER for testing and have been shown to meet the requirements for potency, and sterility.

Viral Clearance Validation

The process has been validated for the ability of the Solvent/Detergent treatment process to inactivate enveloped viruses. Virus validation studies have been performed for HIV, hepatitis B, hepatitis C, as well as the marker viruses BVDV, VSV and Sindbis Virus. Where inactivation rates could be studied, kill was complete within 15 minutes. A summary of the results of these studies is provided in the following table.

Virus	Inactivation ($\log_{10}$)	
VSV	≥5.7 (pH 7.9)	≥5.8 (pH 6.9)
Sindbis Virus	≥5.8 (pH 7.9)	≥5.7 (pH 6.9)
HIV	≥6.0 (pH 7.9)	≥5.0 (pH 6.9)
BVDV	≥6.0	-
HBV	≥6.0	-
HCV	≥5.0	-

D. Labeling

The package insert and container and package labels are in compliance with 21 CFR §§ 201.57, 610.60, 610. 61 and 610.62. The trademark, VIPLAS/SD™ is not known to be in conflict with the trademark of any other biological product.

E. Establishment Inspections

A prelicense establishment inspection of the Melville, NY production facility of V.I. Technologies, Inc. was conducted from December 15 to 19, 1997 by personnel from the Center for Biologics Evaluation and Research, and Team Biologics. A Form FDA-483 listing the inspectional observations was issued at the close of the inspection. The firm provided written responses to these observations on January 23, February 4, February 16, February 26, March 12, March 24, April 2 and April 13, 1998. In this correspondence, the firm described corrective actions that either had been completed or had been undertaken and would be completed in the near future. With respect to the latter, the firm has committed to supply the following additional information post-approval: sanitizer effectiveness studies; specifications and data for environmental monitoring of bag inspection room ongoing vigilance and quarterly reports with respect to particulates in the final product; and the addition of an off-site warehouse for storage of quarantined and released source material and final product.

The corrective actions taken coupled with the post-approval commitments by the firm serve to adequately address the issues noted on the FDA-483 List of Observations.

F. Environmental Assessment

An environmental assessment was filed, reviewed and found to be acceptable. A Finding of No Significant Impact (FONSI) is attached.

IV. Pharmacology/Toxicology

Human plasma causes severe toxic reactions and is not tolerated in animals at dosages approaching those generally used in humans. Since plasma (VIPLAS/SD™ or FFP) can not be administered to animals for long-term toxicology studies, toxicologic evaluation of each of the individual anti-viral treatment agents, Triton X-100 and TNBP, as well as toxicologic studies combining the two agents were performed. For Triton X-100, oral LD_{50}'s determined in rodents range from 1200-1900 mg/kg. IP and IV LD_{50}'s range from 108-150 mg/kg, and the lowest toxic-dose level in mice was determined to be 33.7 mg/kg following intraperitoneal injection in mice, and 15.7 mg/kg in rats. For TNBP, acute toxicity testing revealed a no-effect dose of 45.3 mg/kg in mice and rats, with first intolerance noted at 144 mg/kg in the mice and 143 mg/kg in rats. The LD_{50} is determined to be 605-660 mg/kg in mice, and 610-615 mg/kg in rats. Toxicity studies were also performed with both substances being administered simultaneously. Acute toxicity studies in mice and rats revealed no significant deleterious synergistic effect.

Subchronic and chronic exposure studies in animals suggest that Triton X-100 is non-toxic at 0.17 $mg \cdot kg^{-1} \cdot day^{-1}$. Rats and dogs exposed to 200 $mg \cdot kg^{-1} \cdot day^{-1}$ or 400 $mg \cdot kg^{-1} \cdot day^{-1}$ respectively for 90 days in feed were not adversely affected. Rats and dogs fed 0.27% in the diet for two years showed no ill effects. Subchronic exposure to TNBP for 13 weeks in rabbits demonstrated a no-effect dose of 0.40 $mg \cdot kg^{-1} \cdot day^{-1}$. Actively growing rats were fed a pellet diet containing 0.5% TNBP for 9 weeks. As compared with controls, rats fed a diet including TNBP exhibited lower body weight and increased liver weight expressed as weight *per se* and as weight per 100 g of body weight. No statistically significant difference in the absolute weight of the kidneys or testes was observed, though both were increased when expressed per unit of body weight. No statistically significant differences were observed in blood cell indicators (leukocyte or erythrocyte count, hemoglobin, hematocrit, or mean corpuscular volume) or in 8 of 9 plasma indicators, with the sole exception being a mild increase in blood urea nitrogen.

The combination of TNBP:Triton X-100 (1:5) was tested in rats and dogs for 13 weeks by means of intravenous injection. The following dosages were administered daily:

Dosing of TNBP + Triton X-100 (1:5) to Rats and Dogs for 13-Week Toxicology Testing

Species	TNBP : Triton X-100 $mg \cdot kg^{-1} \cdot day^{-1}$ i.v.	Concentration (ppm) TNBP	Triton X-100
Rat	0.012 : 0.060	1.2	6
	0.060 : 0.300	6	30
	0.300 : 1.500	30	150
Dog	0.013 : 0.065	3	65
	0.050 : 0.250	50	250
	0.500 : 2.500	500	2500

In the case of multiple injections, injection site irritation was prominent in both of the higher dose administrations in both species. No substance-related systemic changes were found in the rats, and no differences were found between treated dogs and the control group except for minimally lower values for hematocrit, hemoglobin and erythrocytes, and higher values for the erythrocyte sedimentation rate. Outside of the local toxicity, no significant systemic toxicity was observed at any dose level tested.

Mutagenic potential testing, including gene mutation test *in vitro* in procaryotes and eurcaryotes, DNA-damage *in vitro* and chromosomal analysis *in vivo* revealed no indication of mutagenic potential. The relevant tests include TNBP micronucleus test in mice; TNBP sister chromatid exchange in CHO cells; TNBP + Triton (1:5), micronucleus test in the rat; TNBP + Triton (1:5), bone marrow cytogenetics in the rat; TNBP + Triton (1:5), Ames mutagenicity; and TNBP + Triton (1:5) mutation study in V79 cells.

Reproduction toxicity testing was performed in two species, the rat and the rabbit, the dams receiving TNBP:Triton X-100 (1:5) intravenously daily during the critical phase of organogenesis (the 6th to 15th day of gestation in the case of the rats and the 6th to the 18th day in the case of the rabbits). The teratogenic studies with rats and rabbits provided no indications of embryotoxic or teratogenic properties.

In considering the amounts of TNBP and Triton X-100 that a patient might be exposed to during treatment with VIPLAS/SD™, patients with TTP, who may be exchanged with several plasma volumes daily, represent the patient population at risk for the exposure to the greatest amounts of VIPLAS/SD™. Thus, a 70-kg patient receiving two plasma volumes per day would receive approximately 0.129 $mg \cdot kg^{-1} \cdot day^{-1}$ of TNBP; over a three-week period of daily treatment, such a patient would receive approximately 63 liters of VIPLAS/SD™, or 2.7 mg/kg of TNBP . In the clinical trial, TTP patients received 28.7 ± 22.4 liters of VIPLAS/SD™ over a similar treatment period. The exposure to TNBP and Triton X-100 is therefore considered to be within the safety margin established by the toxicology studies.

V. Clinical

Eight studies were carried out to determine the safety and effectiveness of VIPLAS/SD™ for the treatment of coagulation factor deficiencies for which no specific coagulation factor concentrate is available and for the treatment of thrombotic thrombocytopenic purpura (TTP).

01 In vivo recovery and half-life
02 Prevention of coagulation factor deficits in patients undergoing serial plasma exchange
03 Control of bleeding in patients with single congenital factor deficiencies
04 Treatment of TTP
05 Immediate reversal of warfarin therapy
06 Coagulopathy due to liver disease
07 Treatment of patients with long prothrombin time
08 Treatment of patients with acquired and congenital factor deficits

In all, 164 patients have received 3992 units of VIPLAS/SD™ during 396 treatment episodes. They are listed by protocol below.

Protocol	No. Patients	No. Episodes	No. Units VIPLAS or FFP
01. Half-life and recovery	3	3	14
02. Serial plasma exchange	8	13	48
03. Congenital factor deficiency	48	138[1,2]	788
04a. Chronic TTP	7[3]	122	348
04b. Acute TTP (VIPLAS/SD™ Arm)	16[4]	19	2193
04b. Acute TTP (FFP- Arm)	10	11	1463
05. Warfarin reversal	7[5]	10	52
06. Coagulopathy in liver disease	44	59	420
07. Long prothombin time (VIPLAS/SD™ Arm)	23[6]	22	87
07. Long prothombin time (FFP Arm)	23	23	89
08. Coagulation factor deficits (VIPLAS/SD™ Arm)	10	10	42
08. Coagulation factor deficits (FFP Arm)	8	8	32
Sum (VIPLAS/SD™ only)	165[7]	396	3992

[1] Includes one patient for which medical record was not available for 2 episodes.
[2] Includes one patient who was transfused for both surgical prophylaxis and active bleeding during one episode.
[3] Includes one patient who received weekly plasma exchanges rather than infusion.
[4] Includes three patients who received both VIPLAS/SD™ and FFP.
[5] One patient not evaluable.
[6] One patient enrolled but not treated.
[7] One patient treated on Protocol I and III.

Recovery data are available from Protocols 01, 02 and 03; Protocols 03, 04 and 05 were designed to evaluate efficacy and Protocols 06, 07 and 08 primarily evaluated safety.

A. Clinical Efficacy

Coagulation factor persistence in plasma

Data on persistence in the circulation after infusion of VIPLAS/SD Pooled Plasma, Solvent/Detergent Treated, have been obtained for coagulation factors V (3 patients) and X (1 patient) in patients congenitally deficient in these factors. In each case, factor levels determined after a 12-24 hour period were consistent with the information available in the literature regarding the half-life of each factor.

Control of bleeding in patients with single congenital factor deficiency

Protocol 03 allowed for open-label treatment for patients with congenital factor deficiency who required treatment for surgical prophylaxis, treatment of an acute bleeding event, or, in the case of Factor XIII deficiency, as routine monthly prophylaxis against bleeding. Only congenitally coagulation factor-deficient patients for whom virally inactivated concentrates were not available were eligible, thus limiting the study to rare forms of hemophilia. Forty-eight patients were treated for 137 episodes, including 47 episodes of surgical prophylaxis, 51 actively bleeding episodes, and 39 routine prophylactic treatments for Factor XIII deficiency.

Congenital Factor Deficiency - Treatment regimens

Factor Deficiency	Prophylaxis		Active Bleeding	
	No Patients	No Episodes	No Patients	No Episodes
Fibrinogen	1	2	1	4
Factor II	1	1	-	-
Factor V	5	7	6	34
Factor VII	4	5	-	-
Factor X	1	4	3	10
Factor XI	22	27	-	-
Factor XIII	4	39	1	2
Passovoy	1	1	-	-
Unconfirmed	-	-	1	1
Sum	39	86	12	51

Prophylaxis in Congenital Factor Deficient Patients

Excluding the factor XIII-deficient patients, who are described separately below, 35 patients were treated in 47 episodes of prophylactic transfusions. The available laboratory data (pre- and post-infusion factor levels, factor level increases, and factor recoveries) are arranged by factor deficiency in the following table. One of the patients

with a single treatment episode had "Passovoy defect" for which no specific deficiency has been identified. Of the remaining 34 patients and 46 episodes, post-infusion factor levels are available from 27 patients and 32 episodes.

Congenital Factor Deficient Patients - Surgical Prophylaxis
Increase in Coagulation Factor

Coagulation Factor	No. of Episodes	Observed Increase per Infusion of 15 mL/kg (mg/dL or u/mL)			Average % Recovery
		Average	Low	High	
Fibrinogen	2	76.6	66.9	86.3	109%
Factor V	6	0.13	0.09	0.17	72%
Factor VII	5	0.15	0.08	0.22	66%
Factor XI	19	0.24	0.10	0.53	94%

On average, a dose of 15 mL/kg of VIPLAS/SD™ resulted in an increase of 77 mg/dL fibrinogen, 0.13 units/mL of factor V, 0.15 u/mL of factor VII, and 0.24 u/mL of factor XI. The recovery of individual coagulation factors was generally high, averaging 66-109%. Lower recoveries occurred in one infusion to a patient who had an inhibitor to factor VII, and one infusion, at a dose of 4 mL/kg, which failed to achieve a factor level considered to be hemostatic.

Of the 47 episodes of prophylactic infusions, clinical outcome is available from 46; the 47th had no surgical procedure. Of these 46 episodes involving 35 patients, hemostasis was maintained in 40 episodes. Bleeding in the remaining six episodes was judged to be due to inadequate dosing or occurred in the late post-operative period. Surgeries successfully performed included dental surgeries, lumbar disc surgeries, exploratory laparotomies, abdominal hysterectomies and oophororectomy, coronary artery bypass grafts and valve replacements, arthroscopic surgeries, parathyroid exploration, transuretheral prostatectomy, facial plastic surgery, cholecystectomy, and removal of a meningioma.

Factor XIII Deficient Patients

Factor XIII deficiency is a rare condition in which patients are typically treated by approximately once-monthly transfusions of FFP in order to preclude bleeding. Four patients with congenital factor XIII deficiency were enrolled in Protocol 03. They were treated prophylactically with 1-2 units of VIPLAS/SD every 21-40 days on average for a period of 2 to 15 months each, and remained asymptomatic.

A fifth factor XIII deficient patient as a routine was treated only for active bleeding. His first treatment with VIPLAS/SD™ was with 4 units to treat a thigh hematoma. The bleeding resolved. Seven months later, he received continuous daily infusions of

VIPLAS/SD™ (35 units over two weeks) to treat a severe right calf bleed and to preclude anterior compartment syndrome. His symptoms gradually resolved.

Actively Bleeding Congenital Factor Deficient Patients

Of the 51 episodes treated, improvement/resolution of bleeding was observed in virtually every case. In the treatment of episodes 11 and 12 of one patient, the patient developed hives with VIPLAS/SD™, received antihistamines, and then received 2 units of FFP.

The indications for treatment and number of units administered are listed in the table below.

Of the 20 episodes where pre- and post-treatment PT and aPTT results are available, a significant shortening was observed in 19. In the one instance where shortening of the PT and aPTT was not observed, the pre-treatment values were normal.

Actively Bleeding Congenital Factor Deficient Patients

Factor deficiency	site of bleeding	number of episodes	units administered in each episode*
Fibrinogen	head trauma	2	5,6
	hemarthrosis	2	7,9
Factor V	hematoma	8	1,1,2,2,2,4,4,38**
	hemarthrosis	7	2,2,2,2,5,6,14
	dental	6	1,1,1,2,2,2
	hematuria	5	1,2,2,2,2
	epistaxis	4	2,2,2,2
	menorrhagia	3	2,2,2
	bleeding ovarian cyst	1	19
Factor X	G.I. bleeding	4	2,2,2,4
	hemarthrosis	3	2,2,2
	dental	1	6
	hematuria	1	2
	menorrhagia	1	2
Factor XIII	hematoma	2	4,35
Unconfirmed	subdural hemorrhage	1	1.9

* most of these administrations were to children, thus the number of transfused units is small; on a mL/kg basis, most children were administered 15-35 mL/kg over a one to several day treatment period
**rectovaginal hematoma

Reversal of warfarin therapy

Seven patients entered the study; however, the surgical procedure for one was canceled as the initial unit of VIPLAS/SD™ was being infused; thus, follow-up on this patient was not completed reducing the number of patients for whom data are available to six. There were 52 units infused during 10 treatment episodes. The following table describes the

reason for reversal of warfarin therapy, whether the patient was bleeding on entrance into the study, the VIPLAS/SD™ dose used, and the physicians' evaluation of efficacy. It can be seen that administration of between 2 and 7 units of VIPLAS/SD™ successfully reversed warfarin therapy in patients with minor bleeding and minor surgery, and larger quantities (11 or 15 units) successfully covered major abdominal surgery.

Reversal of Warfarin Therapy by VIPLAS/SD™ - *Clinical Observations*

Patient - (Episode)	Reason for Infusion	Pre-Infusion Bleeding	Dose		PT (sec)			Perioperative Bleeding (physician's assessment)
			# Units	mL/kg	Pre	Post	Control	
10 - (1)	catheter replacement	no	1	NA[1]	NA	NA	NA	NA[1]
25 - (1)	bleeding from IV site (600 mL in the 8 hours prior to infusion)	yes	7	17	43.6	25	13	bleeding stopped
62 - (1)	prophylaxis for paracentesis	no	5	14	32.8	17.9	13.5	no unusual bleeding
74 - (1)	surgical prophylaxis	no	2	5	38.9	18.9	13.3	no unusual bleeding
94 - (1)	generalized bleeding (unable to determine amount) and prophylaxis for laparoscopic cholecystectomy	yes	3	14	20.6	14.4	13	bleeding resolved; no unusual bleeding
94 - (2)	generalized intra-abdominal bleeding (unable to determine amount) and prophylaxis for laparotomy	yes	7 8	33 38	NA	NA	NA	bleeding resolved; no unusual bleeding[2]
94 - (3)	hemoperitoneum and laparotomy	yes	11	52	20.7	14.4	13	bleeding resolved[3]
106 - (1)	dental surgery	no	3	8	14.5	13.7	14	no unusual bleeding
112 -(1)	dental surgery	no	3	7	15.1	14.6	14	no unusual bleeding
112 - (2)	dental surgery	no	2	5	19.4	17.1	14	no unusual bleeding
average				10	25.7	17	13.5	

footnotes: (1) reversal discontinued and procedure canceled
(2) cover for major abdominal surgery. 7 units infused prior to surgery, 8 units infused after surgery.
(3) cover for major abdominal surgery

Treatment of chronic thrombotic thrombocytopenic purpura

Six patients with chronic TTP were treated with 0.5-3 units of VIPLAS/SD™ given at approximately 21-day intervals, with successful prevention of symptoms for the 6 consecutive cycle follow-up period.

Treatment of acute thrombotic thrombocytopenic purpura

Twenty-six patients with acute TTP were enrolled in a blinded, randomized study comparing VIPLAS/SD™ (N=16) to FFP (N=10). Of the 23 evaluable patients, the mean (± S.D.) volumes per treatment were 2,515 (±991) mL for the VIPLAS/SD™- treated

patients and 2,649 (±742) mL for the FFP-treated patients. The mean number of exchanges for the VIPLAS/SD™-treated patients was 10.3 (± 6.8), compared to 9.7 (±9.3) for the FFP-treated patients, and the total volume infused per patient was 28,523 (±22,417) mL for the VIPLAS/SD™ patients compared to 22,973 (±16,443) mL for the FFP patients. Although no differences were detected between the groups in terms of survival, mean number of remissions per patient, number of relapses per patient or the number of patients achieving remission, the study was underpowered to show equivalence of the two treatments for the treatment of acute TTP.

Patient Mortality - Acute TTP Study

	VIPLAS/SD™	FFP
Death: all enrolled patients	6/16	4/10
Death: all efficacy-evaluable patients	5/13	4/10
Death: evaluable S/P BMT patients	1/1	4/4
Death: evaluable non-S/P BMT patients	4/12	0/6

Secondary Efficacy Parameters

	VIPLAS/SD™ (N=13)	FFP (N=10)
mean total volume of infusions per pt. (mL)	28,523 ± 22,417	22,973 ± 16,443
mean # of treatments per pt.	10.3 ± 6.8	9.7 ± 9.3
mean volume per treatment per pt.	2,515 ± 991	2,649 ± 742
mean # of remissions per pt.	0.6 ± 0.7	0.6 ± 0.5
mean # of relapses per pt.	0.2 ± 0.6	0.1 ± 0.3
# achieved remission	7	6

Treatment of patients with multiple coagulation deficits

This study was established to determine the effectiveness of VIPLAS/SD™ in correcting a prolonged prothrombin time (PT) in patients with acquired coagulation abnormalities due to liver disease, vitamin K deficiency or warfarin therapy and, as secondary goals, to determine whether the correction of the PT results in either cessation of bleeding or allows an invasive procedure to be performed without undue hemorrhage. Forty-six patients of an anticipated 150 were enrolled in the study, of whom 45 were treated (22 VIPLAS/SD™, 23 FFP). Approximately half of the patients were treated for warfarin toxicity, and approximately a third of the patients had exacerbations of chronic liver disease. The protocol design called for eligible patients (those with PT >15 seconds) to be transfused with a single treatment (6-10 mL/kg) of either FFP or VIPLAS/SD™. Four hours after the infusion, another PT was drawn. If the value was >15 seconds and clinical

judgement dictated that the patient would benefit from further therapy, a second infusion was allowed, followed by a third four hours later if the same conditions were met.

Of the 22 VIPLAS/SD™ patients, 12 received only one infusion, 9 received two infusions, and one patient received three infusion. For FFP-treated patients, 14 received one infusion, 3 received two infusions, and 6 received three infusions. Seven of 22 (32%) of the VIPLAS/SD™-treated patients, and 6 of 23 (26%) of the FFP-treated patients corrected their PT to 15 seconds or less after one infusion. The effectiveness of VIPLAS/SD™ or FFP in stopping bleeding in actively bleeding patients was also similar: bleeding was controlled in approximately a third of the patients with either treatment. Treatment as surgical prophylaxis was more successful, with approximately 90% of patients in each treatment group being categorized as treatment successes. However, the study was underpowered to detect a difference between VIPLAS/SD™ and FFP should such a difference have existed.

B. Clinical Safety

Acute adverse experiences

Adverse reactions reported during the clinical studies of VIPLAS/SD™ were similar to those seen with the administration of Fresh Frozen Plasma. Generally, these may include allergic reactions and dyspepsia. As with the intravenous administration of any product, the following reactions may be observed after administration: headache, fever, chills, flushing, nausea, vomiting, lethargy or other manifestations of allergic reactions. During clinical studies with VIPLAS/SD™, 47 of 396 treatment episodes were associated with adverse events. Seventy-four percent of these events were allergic reactions, and all of the allergic reactions were of mild to moderate severity and were responsive to treatment with antihistamines such as diphenhydramine HCl. Other adverse events noted were heartburn/epigastric burning (2 patients), and dysgeusia, and tachycardia/irregular heart beat, congestive heart failure and a poorly formed, loose stool in 1 patient each. In FFP-controlled studies, where most patients had previous exposure to FFP, 11/55 (20%) VIPLAS/SD infusions were complicated by an allergic reaction, as were 14/51 (27%) FFP infusions. It should, however, be noted that these studies were underpowered to detect a difference in safety profile between VIPLAS/SD and FFP should such a difference have existed. Equivalence or superiority cannot be inferred from these studies.

Viral Safety

Although many of the study patients had received multiple transfusions of blood or plasma prior to entrance to the study, the sponsor was able to obtain serologic data on enveloped viral markers (HIV, Hepatitis B, or Hepatitis C) prior to and then 4 to 12 months after VIPLAS/SD™ or FFP infusion for 39 patients. Twenty-six patients were

infused with 1685 units of VIPLAS/SD™ from 41 unique lots and 13 patients were infused with 188 units of FFP. These studies, summarized below, revealed no confirmed instance of seroconversion to HIV, Hepatitis B, or Hepatitis C due to VIPLAS/SD™ infusion in these patients. It should be noted that not all patients were tested for all viruses; in some cases, the patients were known to have been serology positive prior to being treated with study medication, either by prior exposure to the disease or because of prior immunization.

VIRAL STUDIES- Enveloped viruses

Treatment	Units	Lots	Number of patients tested		
			HBV	HCV	HIV
SDP	1685	41	0/14	0/17	0/19*
FFP	188	NA	0/10	0/12	0/7

* One patient subsequently seroconverted to HIV. See text below

Of note is the case of one patient with a factor XIII deficiency who was entered on study in 1992 and received 19 units of VIPLAS/SD™ from 2 separate lots. The patient tested positive for antibodies to HIV-1 in July or August of 1995. PCR testing for HIV was negative for all lots of VIPLAS/SD™ which the patient received. A review of the manufacturing records for these lots revealed no deviations from standard operating procedures. The follow-up investigation concluded that VIPLAS/SD™ was not likely the cause of the seroconversion.

Because SD treatment does not inactivate viruses which do not have a lipid envelope, there is a risk that parvovirus B19 or hepatitis A (HAV) virus might be present in some lots of VIPLAS/SD™. This risk is likely increased by virtue of the pooling of individual plasma units necessary to manufacture VIPLAS/SD™. These viruses have not been transmitted frequently by FFP or other transfusable blood components, which is thought to be due largely to the presence of neutralizing antibodies that are elaborated in individuals shortly after infection. Recipients of VIPLAS/SD™ at a typical dose of 10-15 mL/kg will receive approximately 6,000-9,000 mg of IgG and 480-1800 IU of anti-HAV per dose. This quantity exceeds that which is recommended for HAV prophylaxis when administered as an intramuscular gamma globulin preparation. Similarly high titers of anti-B19 antibody will almost certainly be present in each lot of VIPLAS/SD™ given the prevalence of prior exposure to this virus in the donor population.

For these reasons, VIPLAS/SD™ is not considered to pose an undue risk of transmitting B19 or HAV to recipients of this product. However, this risk was not directly studied during the clinical trials of VIPLAS/SD™, and so appropriate warnings and recommended precautionary measures have been included in the Package Insert (attached). In addition, the manufacturer has committed to performing the following viral safety study during the immediate post-marketing period of the product.

D. Post-Marketing (Phase IV) Study

V. I. Technologies, Inc. has committed to performing the following trial following licensure of the product:

Approximately 200 patients requiring plasma transfusion will be enrolled in a prospective, randomized study in which patients will receive either FFP or VIPLAS/SD™. Patients will be followed for 3 months, and serological status for the non-enveloped viruses hepatitis A and parvovirus B19 will be determined prior to and following therapy. The study will include the use of approximately 10 different lots of VIPLAS/SD™.

VI. Blood Products Advisory Committee

On December 12, 1996, the Blood Products Advisory Committee considered the virological and clinical data submitted in support of the license application for VIPLAS/SD™. The committee voted unanimously, with one abstention, that the apparent safety benefits of VIPLAS/SD™ outweigh any risks, and that no logistical issues preclude approval of the license application for VIPLAS/SD™.

29 APR 98
Thomas J. Lynch, Ph.D. Date
Chair, PLA Review Committee
HFM-340

Laura L. Wood 4/30/98
Laura L. Wood Date
HFM-340

Mark J. Weinstein 4/29/98
Mark J. Weinstein, Ph.D. Date
HFM-340

Mary P. Padgett 30-APR-98
Mary P. Padgett Date
HFM-380

Toby A Silverman MD 4/30/98
Toby A. Silverman, M.D. Date
HFM-380

Richard M. Lewis 7/28/98
Richard M. Lewis, Ph.D. Date
HFM-380

Chinying J. Wang 4/30/98
Chinying J. Wang, Ph.D. Date
HFM-215

Laurie P. Norwood 4/30/98
Laurie P. Norwood Date
Chair, ELA Review Committee
HFM-207

Mary A Malarkey 4/30/98
Mary A Malarkey Date
HFM-207